85. (New) The apparatus of claim 84, wherein said detectable label is a radioactive label, a fluorogenic label, a nuclear magnetic spin resonance label, biotin, or an enzyme that generates a colored product upon contact with a chromogenic substrate.

II. RESPONSE TO OFFICE ACTION

A. State of the Claims

Claims 52-66 were pending at the time of the Action. Claims 67-74 were canceled in response to the election made by the Applicants to prosecute the group I invention, discussed below. Claims 52, 56, 60, and 65-66 have been amended in the Amendment contained herein. Claim 55 and 61 has been canceled without prejudice or disc. New claims 78-85 have been added. Therefore, claims 52-54, 56-60, 62-66, and 78-85 are presently pending. A copy of the amended claims with editing indicia is attached as Appendix A. A clean copy of the presently pending claims is attached as Appendix B.

B. Election/Restrictions

The Action makes note of Applicants' election, without traverse, by Applicants' representative, Mr. Mark B. Wilson, to prosecute the invention of group I. Group I includes claims 52-66, drawn to an apparatus comprising a chamber having an inlet port and outlet port, classified in class 422, subclass 73. Applicants acknowledge the Examiner's withdrawal of claims 67-74 as being drawn to a non-elected invention. Accordingly, claims 67-74 have been canceled without prejudice or disclaimer in the Amendment provided herein.

C. The Claim Rejections Under 35 U.S.C. §112, Second Paragraph, are Overcome

Claims 60, 65, and 67 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. With respect to claim 60, the Examiner asserts that "conditions of low pH" is vague and indefinite. Applicants draw the Examiner's attention to the language of present claim 60, which recites the limitation "wherein the pH is from about pH 1 to about pH 6." Support for this limitation can be found on page 10, lines 3-8 of the Specification.

The Examiner believes the limitation "about 0.01% to about 5%" in claim 65 is vague and confusing because it is unclear how Applicants define the concentration of %. Without conceding that the claim as originally written was indefinite Applicants draw the Examiner's attention to claim 65, which recites the limitation "about 0.01% (weight/volume) to about 5% (weight/volume)." Support for this language can be found in the Specification at page 13, lines 19-20, and page 55, line 20 through page 56, line 29. The Specification also refers to measurement of concentration as weight/volume. See Specification, page 56, lines 14-15. One of skill in the art would understand, from reading these sections of the Specification, that the concentrations in claim 65 are to be interpreted as weight/volume.

Claim 66 is said to share the same indefiniteness as claim 65. Without conceding that the claim as originally written was indefinite, Applicants draw the Examiner's attention to claim 66, which recites "about 1% (weight/volume) to about 4% (weight/volume)." As discussed above, support for this language can be found in the Specification at page 13, lines 19-20, and page 55, line 20 through page 56, line 29. The Specification also refers to measurement of concentration as weight/volume. See Specification, page 56, lines 14-15. One of skill in the art would

understand, from reading these sections of the Specification, that the concentrations in claim 66 are to be interpreted as weight/volume.

D. The Claim Rejections Under 35 U.S.C. §102(b) are Overcome

Claims 52-54, 58-59, and 61 are rejected under 35 U.S.C. §102(b) as being anticipated by Xia *et al.* (Biophysical Journal, 65:1073-1083, 1993). Xia *et al.* is said to teach determination of cellular adhesion of human blood cells by a cylindrical chamber with an inlet and outlet valve in combination with glass coverslips immobilized with the human blood antigen B. Xia *et al.* is also said to teach conducting the assay in pH around 6.5 to 6.8. Applicants traverse this rejection.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). Inherent anticipation requires that the missing descriptive material is "necessarily present," not merely probably or possibly present, in the prior art. *In re Robertson*, 169 F.3d 743, 745, 49 U.S.P.Q.2d 1949, 1950-51 (Fed. Cir. 1999) (citing *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1268 20 U.S.P.Q.2d 1746, 1749 (Fed. Cir. 1991). A rejection based on 35 U.S.C. §102(b) can be overcome by (a) persuasively arguing that the claims are patentably distinguishable from the prior art; (b) amending the claims to patentably distinguish over the prior art, or (c) perfecting priority under 35 U.S.C. §119(e) or §120. *Manual of Patent Examining Procedure* §706.02(b).

Without conceding that the claims as originally written are anticipated, Applicants draw the Examiner's attention to claim 52, which recites "An apparatus comprising a chamber having

an inlet port and an outlet port, said chamber containing an immobilized antigenically-active native Rh blood group antigen protein or peptide." Claim 52 is not anticipated because the limitation "said chamber containing an immobilized antigenically-active native Rh blood group antigen protein or peptide" is not expressly or inherently described in Xia *et al.* As admitted by the Action, Xia *et al.* teaches human blood antigen B. Xia *et al.* makes no mention of use of Rh antigens. Indeed, the Examiner makes the statement that Xia *et al.* "does not specifically teach immobilized Rh antigen on the glass coverslip." Office Action, page 5, paragraph 1. Nor does Xia *et al.* inherently describe use of Rh blood group antigens, as reference to use of Rh blood group antigens is not present in Xia *et al.* Therefore, because Xia *et al.* fails to expressly or inherently disclose each of the limitations of claim 52, it fails to anticipate the invention of claim 52. Because claims 53-54, and 58-59 depend from claim 52, Xia *et al.* fails to anticipate these dependent claims since these claims necessarily incorporate the limitations of claim 52. The rejection of claim 61 is moot since this claim has been canceled. Applicants note that there is adequate support in the Specification for each of the claim limitations.

New claims 78-85, which depend from claim 52, have been added. Xia *et al.* fails to anticipate these claims because, as discussed above, Xia *et al.* fails to expressly or inherently disclose the limitation "said chamber containing an immobilized antigenically-active native Rh blood group antigen protein or peptide."

Accordingly, Applicants request that the rejection of claims 53-54, and 58-59 under 35 U.S.C. §102(b) should be withdrawn.

E. The Claim Rejections Under 35 U.S.C. §103(a) are Overcome

Claims 55-57, 60, and 62-66 are rejected under 35 U.S.C. §103(a) as being unpatentable over Xia *et al.* in view of Suyama *et al.* and Perry *et al.* (U.S. Patent No. 5,087,338). Xia *et al.* is discussed above. Suyama *et al.* is said to teach "purifying Rh polypeptide from red blood cells by immobilized Rh antigen-IgG beads in a buffer containing EDTA, and applying the similar assay to study variant Rh antigens, such as D antigen and c antigen." Office Action, page 5, paragraph 2. Perry *et al.* is said to teach "using zwitterionic buffers for separation of macromolecule proteins because such buffers provide a high field strength and low conductivity to preserve pH value in the process." Office Action, page 5, paragraph 2.

In order to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references, when combined) must teach or suggest all the claim limitations. *Manual of Patent Examining Procedure* §2142. See also *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed Cir. 1991).

The first element necessary to establish a *prima facie* case of obviousness requires that there must be some suggestion or motivation, in the references or in the knowledge generally available to one of ordinary skill in the art, to combine the reference teachings. Applicants assert that there is no such motivation or suggestion to combine these cited references to teach a chamber having an inlet port and an outlet port that contains an immobilized antigenically-active native Rh blood group antigen protein or peptide, nor would such motivation be in the knowledge generally available to one of skill in the art.

Xia *et al.* merely teaches adhesion of red blood cells on glass coverslips. The Examiner states that Xia *et al.* "does not specifically teach immobilized Rh antigen on the glass coverslips." Office Action, page 5, paragraph 1. In addition, the Examiner states that Xia *et al.* "is silent in using various concentration medium buffers and optimized the related pH levels as recited in the instant claims." Office Action, page 5, paragraph 1.

The Examiner points to Suyama *et al.* to provide for the deficiency of Xia *et al.* Suyama *et al.* merely teaches combining red blood cells that have been incubated with polyclonal IgG anti-D plasma, creating ghosts, and then incubating the ghosts with anti-human IgG-agarose beads. The purported Rh(D) antigen-containing polypeptide isolated in Suyama *et al.* is not serologically active in humans. In particular, the end-product polypeptide identified in Suyama *et al.* was not shown to react with human antibody directed against Rh antigen. Therefore, as discussed further below, the end-product polypeptide isolated in Suyama *et al.* was not a native Rh antigen, but a denatured Rh antigen.

In addition, antibody produced in rabbits in response to the polypeptide isolated in Suyama *et al.* did not react with Rh(D)-positive or –negative erythrocites. Moreover, it is not clear in Suyama *et al.* whether the antigen is immobilized or if an antibody was immobilized and then the antigen bound to the antibody. Therefore, the polypeptide isolated in Suyama *et al.* is not an immobilized antigenically-active native Rh blood group antigen protein or peptide.

A characteristic of the invention disclosed herein is to correct a deficiency in the prior art. In particular, a deficiency in the prior art is that "it has not been possible to isolate, store, and immobilize antigenically- (or serologically-) active blood group antigens, and in particular Rh antigen, [which] represents a significant limitation in the medical arts." Specification, page 5, line 28 through page 6, line 1, emphasis added. Therefore, a person skilled in the art would not

have been motivated to modify any of the references to practice the claimed invention as it relates to immobilization of antigenically or serologically active native Rh blood group antigen, since Suyama *et al.* is not clearly directed at immobilizing Rh antigens, and since the isolated polypeptide in Suyama *et al.* was not a antigenically- and serologically-active native Rh blood group protein or peptide. Thus, Suyama *et al.*, by failing to produce an immobilized native Rh blood group antigen protein or peptide that is antigenically and serologically active in humans, has failed to provide motivation to combine the cited references to practice the claimed invention.

Suyama *et al.* also fails to provide any disclosure pertaining to a chamber having an inlet port and an outlet port. There is nothing in Suyama *et al.* or Xia *et al.* that provides a suggestion or motivation to combine the references to provide for a chamber with an inlet port and an outlet port containing an immobilized antigenically-active native Rh blood group antigen protein or peptide.

Perry *et al.* does not correct this deficiency in the cited references. Perry *et al.* merely teaches methods for separating macromolecules using electrophoresis. Perry *et al.* provides no disclosure pertaining to immobilized antigenically-active native Rh blood group protein or peptide, nor does Perry *et al.* teach a chamber having an inlet port and an outlet port. Perry *et al.* merely teaches use of various buffers for electrophoresis and protein separation. The invention disclosed herein is not related to protein separation procedures. Moreover, Perry *et al.* does not teach a requirement for amphoteric or zwitterionic buffers or particular concentrations of these buffers. Rather, Perry *et al.* merely teaches that any of a number of buffers can be used in the disclosed electrophoresis procedures. Consequently, Perry *et al.* fails to correct the deficiency of

Xia *et al.* and Suyama *et al.* in regard to providing any motivation or suggestion to modify the references or combine reference teachings in regard to the claimed invention.

Therefore, there is nothing in Xia *et al.*, Perry *et al.*, or Suyama *et al.* that provides a suggestion or motivation to combine the reference teachings to immobilize antigenically-active native Rh blood group antigen protein or peptide in a chamber having an inlet port and an outlet port. Nor is there any suggestion or motivation to combine the reference teachings to practice the invention from about pH 1 to about pH 6, or to combine the references to immobilize the antigen in the presence of amphoteric or zwitterionic buffers at particular buffer concentrations. Nor would the knowledge generally available to one of ordinary skill in the art provide for the suggestion or motivation to modify or combine the reference teachings to make the claimed invention. Any practice of the claimed invention based on the disclosure of the cited references would require undue experimentation to identify and immobilize an antigenically-active native Rh blood group antigen protein or peptide.

Moreover, there is no reasonable expectation of success of immobilizing antigenically-active native Rh blood group antigen protein or peptide in a chamber having an inlet port and an outlet port. The reasonable expectation of success must both found in the prior art, and not based on Applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

Since Xia *et al.*, Suyama *et al.*, and Perry *et al.* do not teach immobilization of antigenically-active native Rh blood group antigen protein or peptide, it follows that there is no reasonable expectation of success that their disclosures could be used to produce the claimed invention. In addition, there is no reasonable expectation of success that the immobilization of antigenically-active native Rh blood group antigen would be successfully conducted in a

chamber having an inlet port and an outlet port. Thus, the second element necessary to establish a *prima facie* case of obviousness has not been met.

Xia *et al.*, Suyama *et al.*, and Perry *et al.* also fail to teach or suggest all of the claim limitations. The Suyama *et al.* reference discloses the isolation of a denatured Rh polypeptide. This denatured antigen was injected into rabbits to generate antibodies specific to the denatured polypeptide. Although antisera containing these antibodies reacted with denatured polypeptides in ELISA and Western blot formats, the antisera did not react with native Rh antigen.

This result is clearly stated in the Suyama *et al.* reference at page 1623, col. 1, last paragraph, "Antibody produced in rabbits...did not react with either Rh(D)-positive or -negative cells." If the antibody reacted with native Rh(D) antigen, it would bind to Rh(D)-positive cells. The fact that the antibody was unable to bind to Rh(D)-positive cells demonstrates that the Rh(D) antigen purified by Suyama *et al.* was a denatured Rh antigen, not a native Rh antigen.

This conclusion is supported by Suyama *et al.*'s demonstration that the antibody raised against their isolated Rh(D) antigen was able to bind to denatured Rh(D) polypeptide. Figure 2 of Suyama *et al.* shows antibody binding to Rh(D) polypeptide after electroelution from SDS-polyacrylamide gels. SDS (sodium dodecylsulphate) is a well known denaturing detergent. The denatured Rh(D) polypeptide run on SDS-PAGE was able to bind the antibody of Suyama *et al.*, that was made against a denatured Rh(D) polypeptide. The Suyama *et al.* antibody was also shown to bind to denatured Rh(D) polypeptide in ELISA studies against the same electroeluted polypeptide (Table 1).

These results show that the Rh(D) polypeptide purified by Suyama *et al.* was a denatured Rh antigen, not a native Rh antigen. Antibodies made against the Suyama *et al.* Rh(D) polypeptide consistently bound to denatured Rh(D) (Figure 2, Table 1) but were unable to bind

to native Rh(D) (pg. 1623, col. 1, last paragraph). Suyama *et al.* does not disclose the element of an antigenically-active native Rh antigen. Applicants submit that the amended claims are not anticipated by Suyama *et al.* and request withdrawal of the rejection. Therefore, the prior art references fail to teach or suggest all of the claim limitations since the references fail to teach an antigenically-active native Rh blood group antigen protein or peptide.

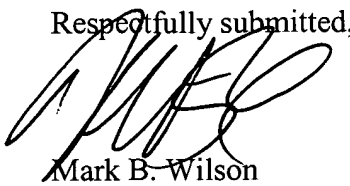
Because the three basic criteria to establish a *prima facie* case of obviousness have not been met, Applicants request that the rejection of claims 55-57, 60, and 62-66 under 35 U.S.C. §103(a) should be withdrawn.

F. Conclusion

Applicants believe that the present document is a full and complete response to the Office Action dated April 8, 2003. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested.

The Examiner is invited to contact the undersigned attorney at (512) 536-3035 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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APPENDIX A
Claim Amendments

52. (Amended) An apparatus comprising a chamber having an inlet port and an outlet port, said chamber containing an immobilized antigenically-active native Rh blood group antigen protein or peptide.

55. (Canceled) The apparatus of claim 54, wherein said mammalian antigen is an Rh antigen.

56. (Amended) The apparatus of claim 54 [55], wherein said Rh antigen is a human Rh antigen or a rabbit homolog of a human Rh antigen.

60. (Amended) The apparatus of claim 52, wherein said protein or peptide is immobilized wherein the pH is from about pH 1 to about pH 6 [under conditions of low pH].

61. (Canceled) The apparatus of claim 60, wherein said pH is from about pH 6 to about pH 1.

65. (Amended) The apparatus of claim 63, wherein said buffer is present at a concentration of from about 0.01% (weight/volume) to about 5% (weight/volume).

66. (Amended) The apparatus of claim 65, wherein said buffer is present at a concentration of from about 1% (weight/volume) to about 4% (weight/volume).

67. (Canceled) A device comprising an antigenically-active blood group antigen protein or peptide.

68. (Canceled) The device of claim 67, wherein said protein or peptide is immobilized.

69. (Canceled) The device of claim 68, wherein said protein or peptide is immobilized under conditions of low pH.

70. (Canceled) The device of claim 69, wherein said pH is of from about pH 6 to about 1.

71. (Canceled) The device of claim 70, wherein said pH is from about pH 2.4 to about pH 4.5.

72. (Canceled) The device of claim 67, wherein said protein or peptide is a mammalian antigen.

73. (Canceled) The device of claim 72, wherein said mammalian antigen is a D antigen, a c antigen, a C antigen, an e antigen, an E antigen, an A antigen, a B antigen, or an F antigen.

74. (Canceled) The device of claim 67, further comprising a glass, plastic, acrylate, methylmethacrylate, Sepharose, agarose, nylon, fiber, or glass wool support.

78. (New) The apparatus of claim 52, wherein the protein or peptide is antigenically-active when the pH is from about pH 1 to about pH 6 during use of the apparatus.

79. (New) The apparatus of claim 78, wherein the pH is from about pH 2.4 to about pH 4.5.

80. (New) The apparatus of claim 52, wherein the protein or peptide is antigenically-active for a period of at least 4 hours during use of the apparatus.

81. (New) The apparatus of claim 64, wherein the buffer is WRA.

82. (New) The apparatus of claim 52, wherein the protein or peptide is immobilized onto a petri dish, a test tube, a vial, a microscope slide, an ELISA plate, a microtiter dish, or a culture plate.

83. (New) The apparatus of claim 52, further comprising an immunoaffinity column or matrix.

84. (New) The apparatus of claim 52, wherein said protein or peptide is linked to a detectable label.

85. (New) The apparatus of claim 84, wherein said detectable label is a radioactive label, a fluorogenic label, a nuclear magnetic spin resonance label, biotin, or an enzyme that generates a colored product upon contact with a chromogenic substrate.

APPENDIX B
Pending Claims

52. An apparatus comprising a chamber having an inlet port and an outlet port, said chamber containing an immobilized antigenically-active native Rh blood group antigen protein or peptide.

53. The apparatus of claim 52, wherein said chamber is cylindrical.

54. The apparatus of claim 52, wherein said protein or peptide is a mammalian antigen.

56. The apparatus of claim 54, wherein said Rh antigen is a human Rh antigen or a rabbit homolog of a human Rh antigen.

57. The apparatus of claim 56, wherein said antigen is a D antigen, a c antigen, a C antigen, an e antigen, an E antigen, an A antigen, a B antigen, or an F antigen.

58. The apparatus of claim 52, further comprising a pump.

59. The apparatus of claim 52, wherein said protein or peptide is immobilized onto a glass, plastic, acrylate, methylmethacrylate, Sepharose, agarose, nylon, fiber, or glass wool support.

60. The apparatus of claim 52, wherein said protein or peptide is immobilized wherein the pH is from about pH 1 to about pH 6.

62. The apparatus of claim 61, wherein said pH is from about pH 2.4 to about pH 4.5.

63. The apparatus of claim 52, wherein said antigen is immobilized in the presence of an amphoteric or zwitterionic buffer.

64. The apparatus of claim 63, wherein said buffer is EDTA, WRA, MOPS, HEPES, glycine, alanine, Bis-Propane or Bis-Tris.

65. The apparatus of claim 63, wherein said buffer is present at a concentration of from about 0.01% (weight/volume) to about 5% (weight/volume).

66. The apparatus of claim 65, wherein said buffer is present at a concentration of from about 1% (weight/volume) to about 4% (weight/volume).

78. The apparatus of claim 52, wherein the protein or peptide is antigenically-active when the pH is from about pH 1 to about pH 6 during use of the apparatus.

79. The apparatus of claim 78, wherein the pH is from about pH 2.4 to about pH 4.5.

80. The apparatus of claim 52, wherein the protein or peptide is antigenically-active for a period of at least 4 hours during use of the apparatus.

81. The apparatus of claim 64, wherein the buffer is WRA.

82. The apparatus of claim 52, wherein the protein or peptide is immobilized onto a petri dish, a test tube, a vial, a microscope slide, an ELISA plate, a microtiter dish, or a culture plate.

83. The apparatus of claim 52, further comprising an immunoaffinity column or matrix.

84. The apparatus of claim 52, wherein said protein or peptide is linked to a detectable label.

85. The apparatus of claim 84, wherein said detectable label is a radioactive label, a fluorogenic label, a nuclear magnetic spin resonance label, biotin, or an enzyme that generates a colored product upon contact with a chromogenic substrate.